REMARKS

Applicants respectfully request reconsideration and withdrawal of the outstanding objections and rejections, in light of the foregoing amendments and following remarks.

Status of Claims

Claims 1-58, 60-61, 63-64, 95-123 and 125 have been canceled.

Claims 59, 62 and 65-67 have been amended.

Claims 59, 62, 65-94 and 124 are pending for the Examiner's consideration.

For the reasons that follow, Applicants believe all Claims are now in condition for allowance.

Amendments of Claims

In compliance with the restriction requirement, Claims 1-58, 95-123 and 125 have been canceled as being drawn to a nonelected invention.

Solely in order to expedite prosecution of the present application, Applicants have canceled Claims 60-61 and 63-64 and amended Claims 59, 62 and 65-67. Neither cancellation of Claims 60-61 and 63-64 nor amendment of Claims 59, 62 and 65-67 constitutes any admission regarding the subject matter. Applicants reserve a right to pursue this subject matter in this or other application(s).

Applicants have amended Claim 59 and 65-67 to specify the claimed method as a method for treating neuropathic pain. Support for this amendment of Claims 59, 62 and 65-67 can be found, for example, in the specification at page 14, lines 7-26, Examples 1-3, and in the originally-filed Claim 60.

Applicants have further amended Claim 59 to include "a mammal" instead of "a subject" in the claim language. Support for this amendment of Claim 59 can be found, for example, in the specification at page 74, lines 20-22.

Applicants have yet further amended Claim 59 to include the proviso that

when W is OH, then J cannot be Me, OMe, SMe, or SO_2Me;

when W is NHOH, then J cannot be Me or OEt; and

when W is NR_2OR_1, wherein R_1 is H, C_{1-8} alkyl, C_{3-8} cycloalkyl, phenyl; R_2 is H, phenyl, C_{1-4} alkyl, C_{3-8} cycloalkyl, then J cannot be SR_C, OR_C, SO_2R_C, SOR_C, C_{1-8} alkyl, or -M'E'G'.

No new matter was added by way of these amendments. The Examiner is hereby requested to enter these amendments.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 59-94 and 124 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly being not enabling for treating any chronic pain caused by any diseases/disorders.

Applicants maintain that the specification is enabling for the originally-filed Claims 59-94 and 124 for the same reasons of record in the previous Response to February 17, 2004 Office Action.

Applicants reiterate that the specification specifically teaches the use of MEK inhibitors for treating chronic pain, for example, at page 14, lines 7-24:

"The effect of the MEK inhibitor PD 198306 has been investigated in two animal models of neuropathic pain by assessing static allodynia with von Frey hairs.

Oral administration of PD 198306 (3-30mg/kg) had no effect in the model of chronic constriction injury of the sciatic nerve (CCI). However, after repeated administration (3 doses over two days) it had a transient effect in the diabetic neuropathy model (streptozocin). This may be due to disorders of the blood-brain barrier induced by the diabetic condition in these animals, thus allowing central action of the compound. Intrathecal administration of PD 198306 (1-30μg) dose-dependently blocked static allodynia in both the streptozocin and the CCI models of neuropathic pain, with minimum effective doses (MED) of 3 and 10μg respectively. The highest dose used (30μg) totally blocked the maintenance of static allodynia, for up to 1h. Intraplantar administration of PD 198306 (3mg/100μl) at a dose 100-fold higher than the dose shown to be effective intrathecally (30μg/10μl) had no effect on static allodynia in either of the neuropathic pain models. This finding confirms the lack of effect seen after systemic administration and suggests a central site of action for the compound.

From this study we can suggest the *use of MEK inhibitors* as potential new therapeutic tools *for chronic pain*." Emphasis added.

The specification provides the references which indicate that the animal models disclosed in Examples 1-3 are adequate for chronic pain assessment (*Courteix C, Eschalier A and Lavarenne J. Streptozocin –induced rats: behavioural evidence for a model of chronic pain. Pain 1993;53:81-8*) in man (*Bennett GJ, Xie Y-K. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. Pain 1988;33:87-107*). Page 91, lines 24—27. Emphasis added.

Therefore, the specification provides the necessary guidelines for a person skilled in the art how to make and use the claimed invention directed to a method for treating chronic pain.

However, solely in order to expedite prosecution of the present application, Applicants have amended Claims 59 and 65-67 to specify the claimed method as a method for treating neuropathic pain.

Applicants respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 59-94 and 124 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for recitation "subject."

Applicants maintain that the originally-filed Claims 59-94 and 124 satisfy the requirements of 35 U.S.C. § 112, second paragraph for the same reasons of record in the previous Response to February 17, 2004 Office Action.

However, solely in order to expedite prosecution of the present application, Applicants have amended Claim 59 to include "a mammal" instead of "a subject" in the claim language.

Applicants respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. § 102(b)

Connor et al., EP 0 316 630 A ("Connor")

Claims 59, 62, 65-66, 69 and 71 were rejected under 35 U.S.C. § 102(b) as anticipated by Connor for the reasons set forth on pages 10-11 of the Office Action.

Applicants maintain that the originally-filed Claims 59, 62, 65-66, 69 and 71 satisfy the requirements of 35 U.S.C. § 102(b) for the same reasons of record in the previous Response to February 17, 2004 Office Action.

Applicants reiterate that "...for anticipation under 35 U.S.C. § 102, the reference must teach each and every aspect of the invention either explicitly or impliedly. Any feature not directly taught must be inherently present." MPEP 706.02.

The present invention is directed to a method for treating chronic pain, which method comprises administering to a subject in need of such treatment a composition comprising a MEK inhibitor.

The Examiner correctly pointed out that Connor teaches a method for treating a condition which is affected by inhibition of 5-lipoxygenase or cyclooxygenase in a mammal suffering from the condition. Nowhere Connor discloses a MEK inhibitor useful for treating pain. Since Connor does not disclose the recited MEK inhibitor, there can be no anticipation.

However, solely in order to expedite prosecution of the present application, Applicants have amended Claim 59 to include the proviso that when W is NR_2OR_1, wherein R_1 is H, C_{1-8} alkyl, C_{3-8} cycloalkyl, phenyl; R_2 is H, phenyl, C_{1-4} alkyl, C_{3-8} cycloalkyl, then J cannot be SR_C, OR_C, SO_2R_C, SOR_C, C_{1-8} alkyl, or -M'E'G', which proviso expressly excludes the compounds of Connor from the language of the amended Claim 59.

Accordingly, Applicants respectfully request that the rejection under § 102 over Connor be withdrawn.

Fujimura et al. CA 69: 35685d ("Fujimura")

Claims 59, 62, 65 and 70 were rejected under 35 U.S.C. § 102(b) as anticipated by Fujimura for the reasons set forth on pages 11-12 of the Office Action.

Applicants contend that Claims 59, 62, 65 and 70 satisfy the requirements of 35 U.S.C. § 102(b) for the same reasons as set forth above in regard to Connor.

Nowhere Fujimura discloses a MEK inhibitor useful for treating pain. Since Fujimura does not disclose the recited MEK inhibitor, there can be no anticipation.

However, solely in order to expedite prosecution of the present application, Applicants have amended Claim 59 to include the proviso that when W is NHOH, then J cannot be Me or OEt, which proviso expressly excludes the compounds of Fujimura from the language of the amended Claim 59.

Accordingly, Applicants respectfully request that the rejection under § 102 over Fujimura be withdrawn.

Morkhort et al. CA 76:121461 ("Morkhort")

Claims 59, 62, 65 and 69 were rejected under 35 U.S.C. § 102(b) as anticipated by Morkhort for the reasons set forth on page 12 of the Office Action.

Applicants contend that Claims 59, 62, 65 and 69 satisfy the requirements of 35 U.S.C. § 102(b) for the same reasons as set forth above in regard to Connor.

Nowhere Morkhort discloses a MEK inhibitor useful for treating pain. Since Morkhort does not disclose the recited MEK inhibitor, there can be no anticipation.

However, solely in order to expedite prosecution of the present application, Applicants have amended Claim 59 to include the proviso that when W is OH, then J cannot be Me, OMe, or SMe, which proviso expressly excludes the compounds of Morkhort from the language of the amended Claim 59.

Accordingly, Applicants respectfully request that the rejection under § 102 over Morkhort be withdrawn.

Hiroshi et al. CA 69: 35685d ("Hiroshi")

Claims 59, 62, 65, 69 and 77 were rejected under 35 U.S.C. § 102(b) as anticipated by Hiroshi for the reasons set forth on pages 12-13 of the Office Action.

Applicants contend that Claims 59, 62, 65, 69 and 77 satisfy the requirements of 35 U.S.C. § 102(b) for the same reasons as set forth above in regard to Connor.

Nowhere Hiroshi discloses a MEK inhibitor useful for treating pain. Since Hiroshi does not disclose the recited MEK inhibitor, there can be no anticipation.

However, solely in order to expedite prosecution of the present application, Applicants have amended Claim 59 to include the proviso that when W is OH, then J cannot be SO_2Me, which proviso expressly excludes the compound of Hiroshi from the language of the amended Claim 59.

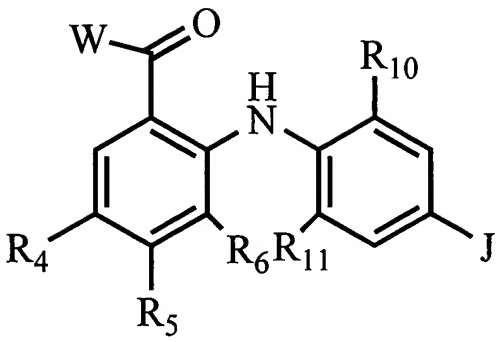
Accordingly, Applicants respectfully request that the rejection under § 102 over Hiroshi be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 59-94 and 124 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over WO 99/01421 in view of Walker et al. British J. Clin. Pharm., 1993, v. 36, pp.417-425 ("Walker") and Ma et al. Brain Res., 1991, v. 566, pp. 95-102 ("Ma") for the reasons set forth on page 13-16 of the Office Action.

Applicants maintain that the originally-filed Claims 59-94 and 124 satisfy the requirements of 35 U.S.C. § 103(a) for the same reasons of record in the previous Response to February 17, 2004 Office Action.

Applicants reiterate that the present invention is directed to a method for treating chronic pain, which method comprises administering to a subject in need of such treatment a composition comprising a MEK inhibitor selected from a compound of formula (I)B:



(I)B

wherein J is SR_C, OR_C, SO_2R_C, SOR_C, $SO_2NR_DR_E$, C $_{1-8}$ alkyl, C $_{3-8}$ alkenyl, C $_{3-8}$ alkynyl, C $_{3-8}$ cycloalkyl, C $_{5-8}$ cycloalkenyl, phenyl, (C $_{3-8}$ cycloalkyl)C $_{1-4}$ alkyl, (C $_{3-8}$ cycloalkyl)C $_{3-4}$ alkenyl, (C $_{3-8}$ cycloalkyl)C $_{3-4}$ alkynyl, C $_{3-8}$ heterocyclic radical, (C $_{3-8}$ heterocyclic radical)C $_{1-4}$ alkyl, -M'E'G', (heterocyclic radical)-M'-E'-G', or (cycloalkyl)-M'-E'-G';

M' is O, SO, SO_2, NR_E, (CO)NR_E, NR_E (CO), SO_2NR_E, NR_ESO_2, or CH_2;

E' is absent (a covalent bond), $(CH_2)_{1-4}$ or $(CH_2)_m O(CH_2)_p$ where $1 \leq$ (each of m and p independently) ≤ 3 and $2 \leq (m + p) \leq 4$;

G' is OR_3, SO_2R_C, or NR_FR_G; provided that where p = 1, then G' is H;

each of R_C, R_D, R_E, R_F and R_G is independently selected from H, C $_{1-6}$ alkyl, C $_{3-4}$ alkenyl, C $_{3-4}$ alkynyl, C $_{3-6}$ cycloalkyl, C $_{3-6}$ heterocyclic radical, and phenyl; NR_FR_G and NR_DR_E can each also independently be selected from morpholinyl, pyrazinyl, piperazinyl, pyrrolidinyl, or piperadinyl;

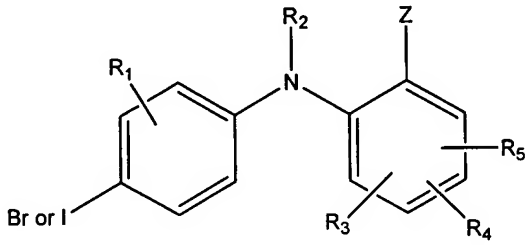
Thus, to establish a prima facie case of obviousness, the Examiner must show: (1) some suggestion or motivation for one of ordinary skill in the art to modify or combine reference teachings in a way that would provide a method for treating chronic pain, which method comprises administering to a subject in need of such treatment a composition comprising a MEK inhibitor selected from a compound of formula (I)B; and (2) a reasonable expectation of success that administering to a subject such a composition comprising a MEK inhibitor selected from a compound of formula (I)B will provide a method for treating chronic pain. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and must not be based on the applicant's disclosure. Finally, the prior art reference (or references when combined) must teach or suggest all claim limitations. *In*

re Vaeck, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); *In re Dance*, 160 F.3d 1339 (Fed. Cir. 1998); M.P.E.P. 2143.

The first requirement goes to the question of motivation, and refers to a well established holding from earlier case law that there must be some logical reason at the time of the invention for modifying the cited references along the lines of the invention; otherwise the use of the teachings as evidence of non-obviousness will entail prohibited hindsight. *Ex parte Stauber and Eberle*, 208 U.S.P.Q. 945, 946 (Bd. App. 1980).

In the present case, Applicants maintain that there is simply no motivation to combine the teachings of WO 99/01421 with those of Walker and Ma. Furthermore, even in combination, the WO 99/01421, Walker and Ma references do not teach or suggest all the claim limitations, including a composition comprising a MEK inhibitor selected from a compound of formula (I)B. Finally, Applicants believe that the WO 99/01421, Walker and Ma references are irrelevant to the subject matter of the present invention for the reasons set forth below.

WO 99/01421 discloses compounds defined by Formula



The Examiner pointed out that WO 99/01421 does not disclose the employment of the particular MEK inhibitors in methods of treating chronic pain. Furthermore, Applicants note that the genus disclosed in WO 99/01421 specifically teaches iodine or bromine for J substituent. WO 99/01421 does not disclose, teach or suggest any compounds having a J substituent of compounds of formula (I)B. Nor does this reference teach or suggest modifying the compounds taught therein to arrive at the class of compounds of compositions administering to a subject for treating chronic pain of the claimed methods of the present invention.

Ma limits its teaching to studies of the release of enkephalins (ENK) and β-EP in brain nuclei. Ma mentions "MEK" in the following context.

"Previous studies using the technique of microinjection into brain nuclei indicated that the periaqueductal gray (PAG), nucleus accumbens, habenula and amygdala play an essential role in pain modulation and that these nuclei possibly act through a 'mesolimbic neural loop' to exert an analgesic effect, in which *Met-enkephalin (MEK)* and β-endorphin (β-EP) have been implicated as the two major opioid peptides involved in antinociception." Abstract; emphasis added.

Ma is irrelevant to the subject matter of the present invention, which invention targeted MEK enzymes, dual specificity kinases, involved in, for example, immunomodulation, inflammation, and proliferative diseases such as cancer and restenosis as indicated at page 12, lines 18-20 of the specification. Contrary to the Office's allegation that "the meaning of "MEK" is not seen to be clearly defined in the specification herein," the specification provides the necessary details about the MEK strategic position in mitogen-activated protein kinase intracellular signaling cascades. See, for example, page 12, line 16 through page 14, line 6.

Walker does not cure the deficiencies of Ma because Walker limits its teachings to establishing an experimental pain model that could distinguish the analgesic effects of ibuprofen and diflunisal treatment from placebo in human volunteers.

Thus, the Office Action did not establish a *prima facia* case of obviousness in the present situation. Applicants respectfully request that the rejection under § 103 be withdrawn.

Conclusion

Applicants believe all claims are now in condition for allowance. Should there be any issues that have not been addressed to the Examiners satisfaction, Applicants invite the Examiner to contact the undersigned attorney.

Applicants do not believe any fees are due in connection with this response. If any fees are due in connection with this response, please charge such fees to Deposit Account No. 500329.

Respectfully submitted,

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Date: February 11, 2005

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